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Establishing Clinical Similarity for Similar Biotherapeutic Products – The Concept of Sensitive Populations

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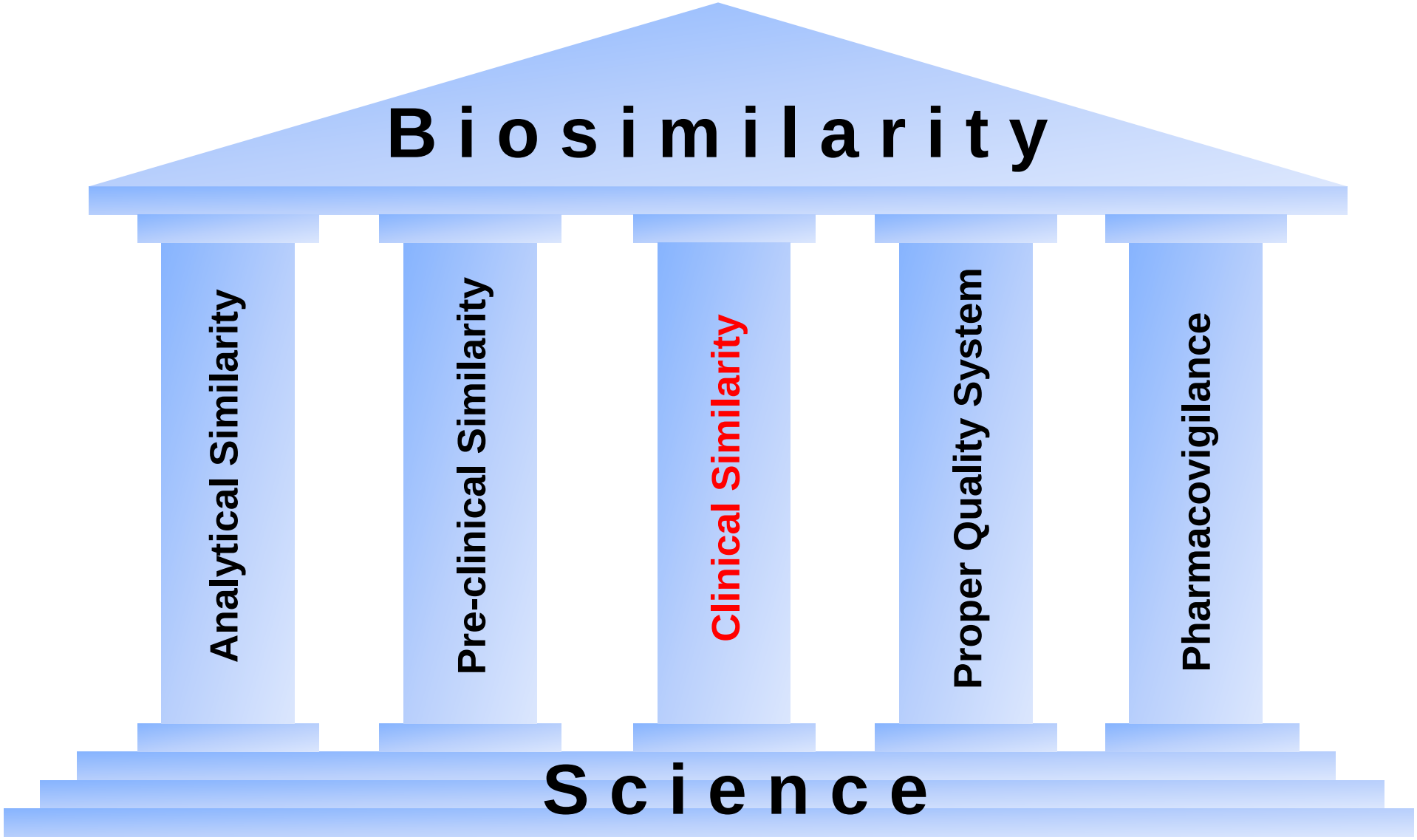
The concept of biosimilarity is built on five indispensible pillars:



What are the fundamental principles establishing clinical biosimilarity?

- **Ensuring that the previously proven safety and efficacy of the drug is conserved**
- **Demonstrating clinical similarity of the SBP compared to the RBP (efficacy, safety and immunogenicity), not patient benefit per se**
- **All studies have to be planned and executed with the intention to detect any potential differences between SBP and RBP and to determine the relevance of such differences, should they occur**

Adopted from: Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies. Non-clinical and Clinical Issues. EMA/CHMP/BMWP/403543/2010

The clinical development requirements for SBPs are different compared to the ones that have been applied for the RBP

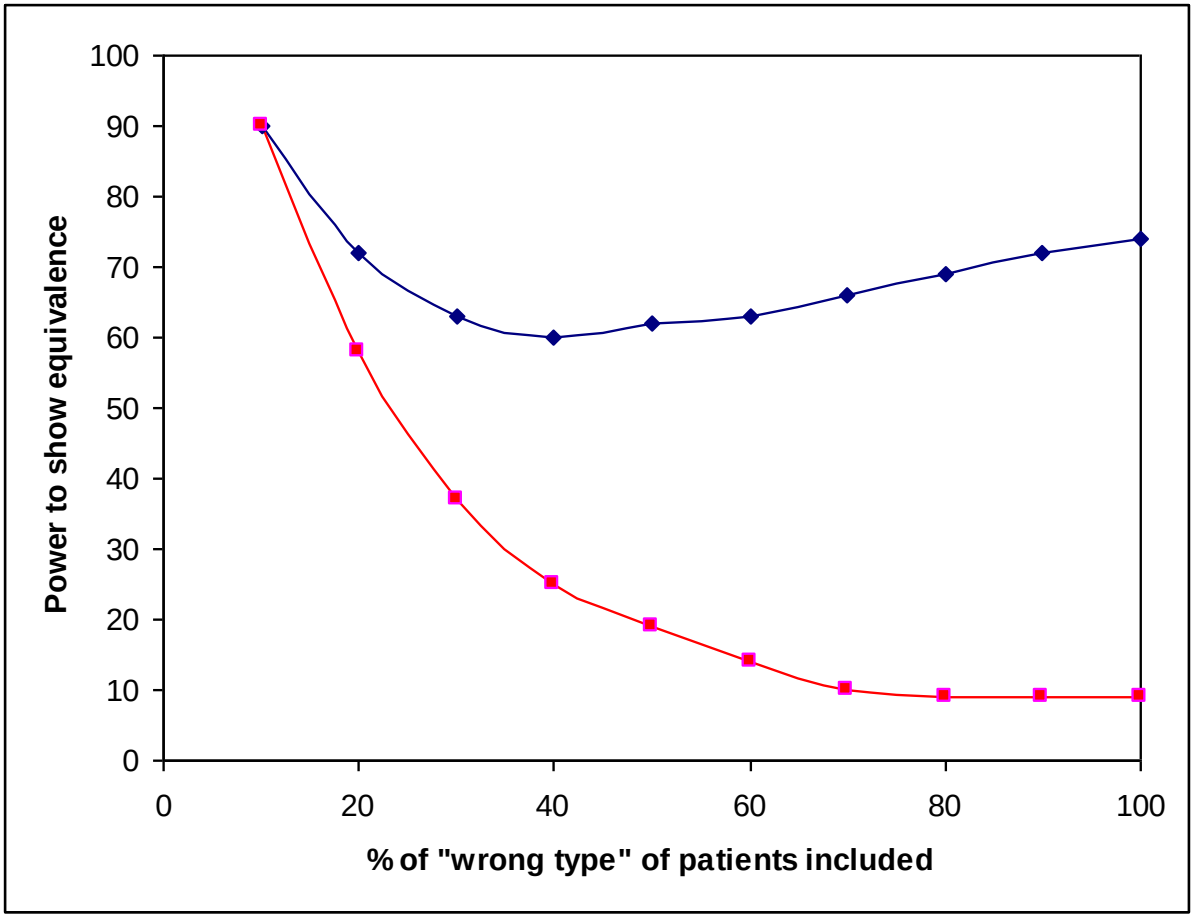
Aspects of development	Biosimilar	Innovator
Patient population	**Sensitive and homogeneous (patients are *models*)**	Any
Clinical design	Comparative versus innovator, normally equivalence	Superiority vs standard of care (SoC*)
Study endpoints	**Sensitive** Clinically validated PD markers	Clinical outcomes data or accepted/established surrogates (e.g. OS and PFS)
Safety	Similar safety profile to innovator; no new findings	Acceptable benefit/risk profile versus SoC*
Immunogenicity	Similar immunogenicity profile to innovator	Acceptable risk/benefit profile versus SoC*
Extrapolation	**Possible if scientifically justified**	Full development Not allowed

* In some cases SoC may not exist

What is a sensitive and homogeneous population? What are sensitive endpoints?

- The idea is to study the biosimilar in the population of patients in whom – *if there is a difference between biosimilar and reference product* – that difference will most easily be detected
  - for example, we have a treatment that works in 60% of patients. If we were able to identify who are the "responder" patients, then we would target treating just those patients
- Activity rather that treatment outcome endpoints likely to be selected to demonstrate clinical similarity
  - The selected endpoints must have a large effect size to set up appropriate confidence intervals

A case study: Wrong patient selection leads to wrong clinical similarity conclusion



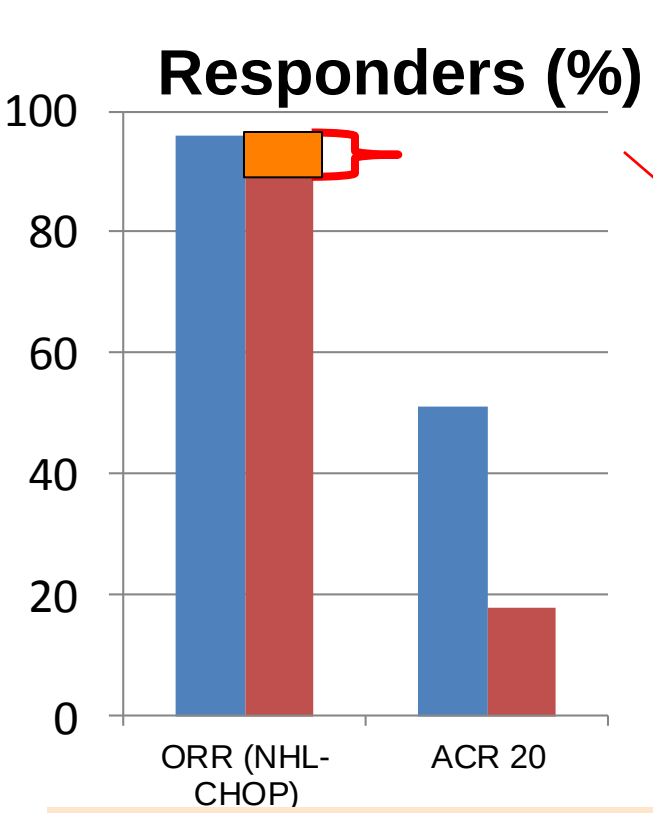
Treatment works in 30 % of the patients

Treatment works in 60 % of the patients

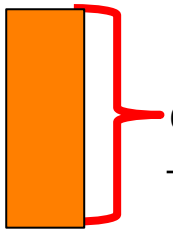
A case study: What are sensitive clinical endpoints for the demonstration of similarity?

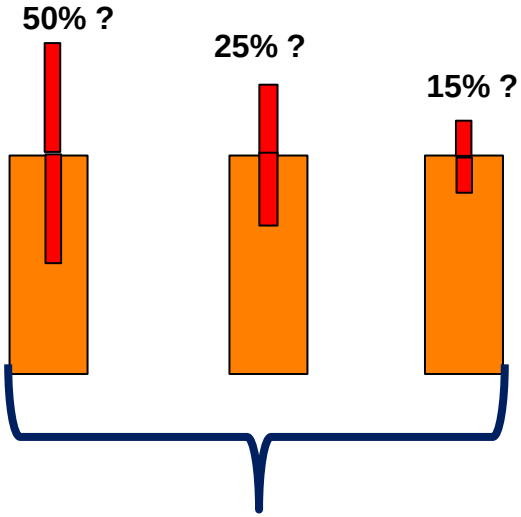
Indications approved for rituximab	ORR Control	ORR Active	Effect Size	Reference
NHL follicular Induction (CHOP)	90%	96%	6%	SPC (GLSG) Hiddemann
NHL follicular Induction (CVP)	10 %	41%	31%	SPC (CR)
NHL follicular relapsed (CHOP)	74%	87%	13%	SPC
NHL DLBCL Induction	76%	84%	8%	SPC (CR)
CLL	72 %	86 %	14%	SPC
Rheumatoid Arthritis (TNF-IR)	18%	51%	33%	SPC (ACR20)

Overall Response Rate is not a sensitive endpoint in Follicular Lymphoma patients treated with R-CHOP



By what fraction of MabThera's effect size can the biosimilar treatment effect differ and still be considered clinically similar?





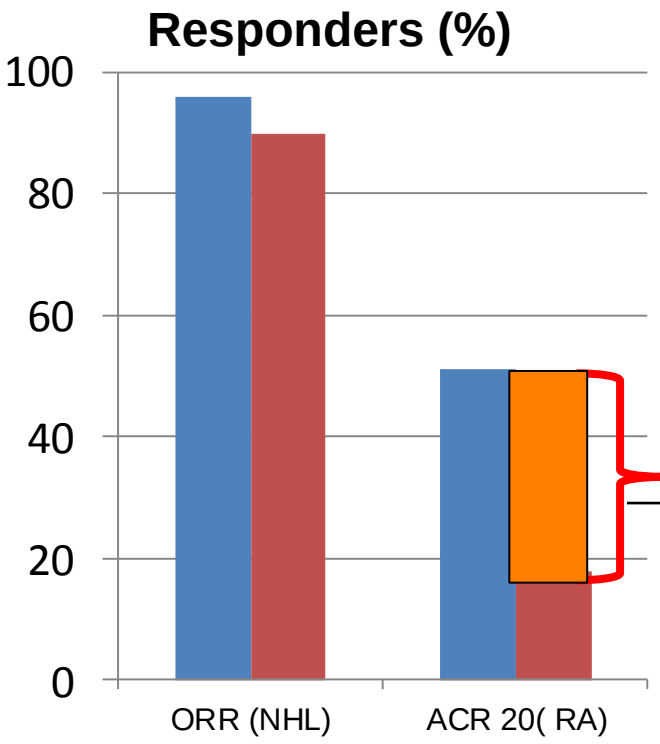
If 25% of the effect size is chosen

Then the comparability margin = 0.25 x 6%= 1.5%

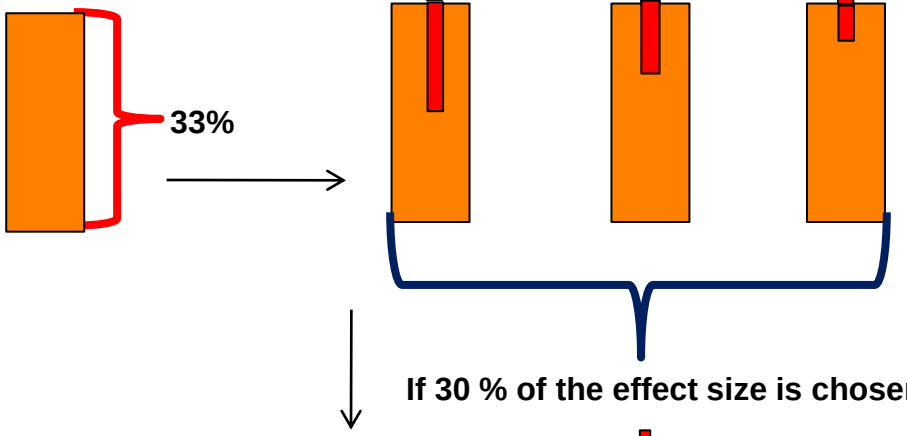
Therefore, if the difference in ORR responses between Mabthera and biosimilar is statistically significantly less than 1.5%, the biosimilar is within the comparability margin

Sample size = 4,000 per group

ACR20 is a sensitive endpoint in AR patients treated with MabThera (TNF IR)



By what fraction of MabThera's effect size can the biosimilar treatment effect differ and still be considered clinically similar?



If 30 % of the effect size is chosen

Then the comparability margin = 0.30 x 33%= 10 %

Therefore if difference in ACR20 between Mabthera and the biosimilar is statistically signicantly less than 10%, the biosimilar is within the comparability margin

Sample size = 250 per group

When is extrapolation justified?

- The biosimilar development needs to **manage the risk associated with extrapolation of clinical data** to indications not practically studied during the similarity assessment which means:
  - The **mode of action has to be the same** in the indication to be extrapolated
  - A step wise approach with clinical trials **assessing the different clinical parameters in the most sensitive population** is the basis.
  - The **risk for immunogenicity** in different patient populations **has to be assessed critically**

A risk identification and -assessment strategy is needed on immunogenicity for NBEs and Biosimilar MAbs

- **The standard immunogenicity testing program may be reduced with thorough justification, or may need to be intensified, depending on the level of risk identified**

- **Risk drivers** e.g.:
  - **Sensitivity of the methodology** to detect antibodies against mAbs
  - **Sensitivity to detect clinical consequences** (e.g. mAb trough concentration, PD parameters and response to mAb treatment)
  - Vulnerability of the patient population, therapeutic index, auto-immune status, **use of immuno-suppressant co-medication etc**.

EMA guidelines on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use and on similar biological medicinal products containing monoclonal antibodies - non-clinical and clinical issues

Case study: Immunogenicity of therapeutic Mabs

Antibody Class	Therapeutic Area	MAb	(Main) Indication	Frequency [Overall, w, w/o Co-Medication]	Consequences: (…): Trend; (…, Single Cases): Influence in Single Patients		
					Pharmacokinetics	Efficacy	Safety
Human	CID	Ad	[Overall]	[b]	CL ↑	Efficacy ↓	No apparent effect
			Rheumatoid arthritis	5.5%, 0.6% w, 12.4% w/o MTX			
			PJIA	15.8%, 5.9% w, 25.6% w/o MTX			
			Psoriatic arthritis	10.1%, 7.1% w, 13.5% w/o MTX			
			Ankylosing spondylitis	8.3%, 5.3% w, 8.6% w/o MTX			
			Crohn's disease	2.6%			
			Psoriasis	8.4%			
		Us	Plaque psoriasis	5%[b]	(CL ↑)	(Efficacy ↓)	No apparent effect
	Onc/Haem	Pa	Colorectal cancer	0.2, 1.6%[b] Up to 3.8%, persistent 2.0%[a]	No apparent effect	No apparent effect	No apparent effect
Fusion proteins	CID	Ab	Rheumatoid arthritis	2.8%, up to 7.4%[b, a]	No apparent effect	Not yet finally evaluated	Not yet finally evaluated
		Et	[Overall]	[b]	NA	No apparent effect	No apparent effect
			Rheumatoid arthritis	6%			
			Psoriatic arthritis	7.5%			
			Ankylosing spondylitis	2%			
			Plaque psoriasis	7%			
			Psoriasis	Up to 9%			

Based on information from the European Public Assessment Reports; mAbs are abbreviated to their first two letters, cf. Table 2.
[a]Marketing authorisation suspended by European Commission.
References: a: scientific discussion/assessment report; b: product information.
AR/HSR: administration-related/hypersensitivity reactions; B-CLL: B-cell chronic lymphocytic leukemia; CID: chronic inflammatory diseases; CL: clearance; IST: mmunosuppressive therapy; MTX: methotrexate; NA: not available, no statement; Onc/Haem: oncology/haematology; PJIA: polyarticular juvenile idiopathic arthritis; w, w/o: with, vithout.

***R. Niebecker et. al Current Drug Safety*, 2010, *5*, 275-286 275**
Safety of Therapeutic Monoclonal Antibodies

Case study: Immunogenicity of therapeutic Mabs

- **Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis patients in a dose dependent manner**

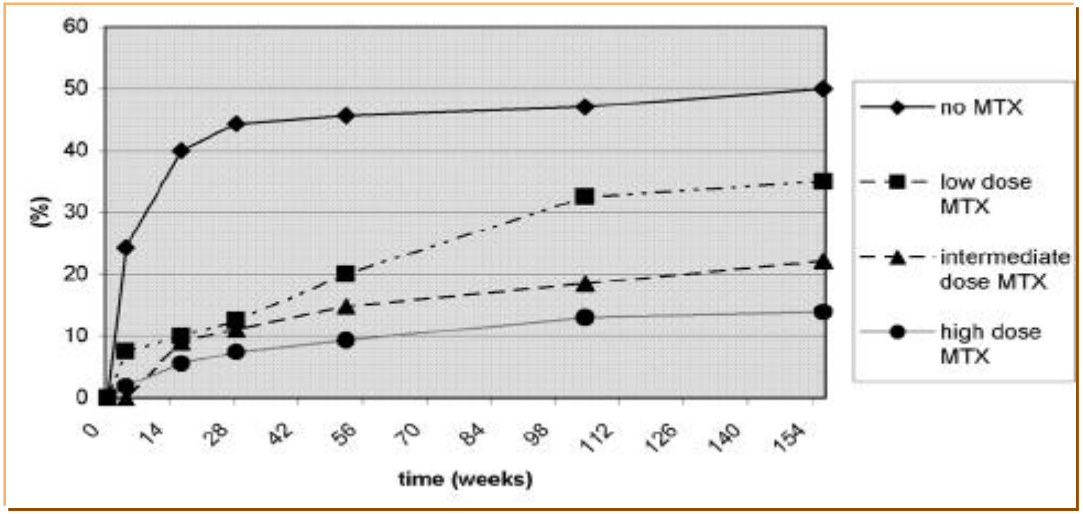
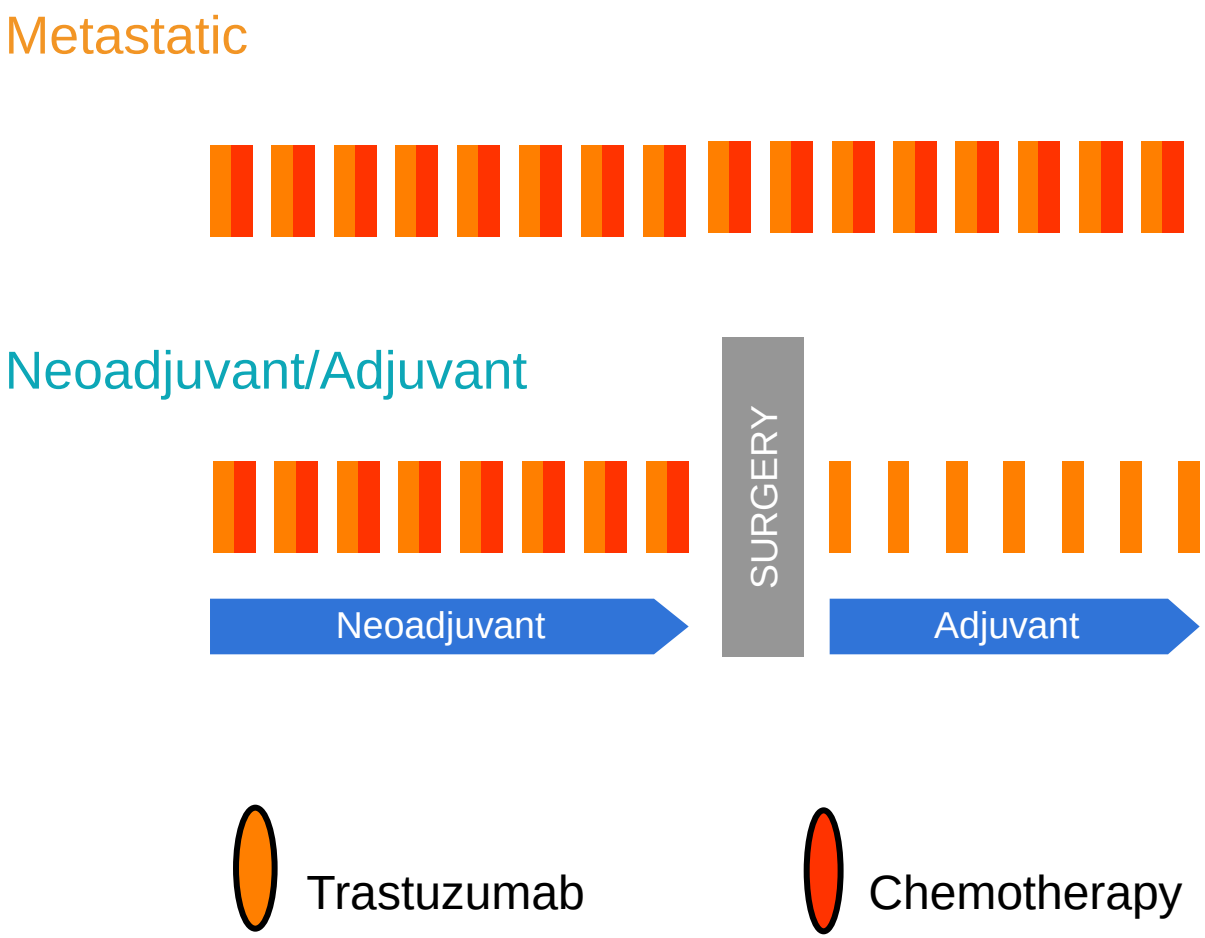


Figure 1 Percentage of patients developing antiadalimumab antibodies (AAA) per baseline methotrexate (MTX) dose group. No MTX (0 mg/week, n=70), low dose MTX (5–10 mg/week, n=40), intermediate dose MTX (12.5–20 mg/week, n=54), or high dose MTX (≥22.5 mg/week, n=108).

Establishing similarity for a trastuzumab biosimilar candidate: What is the right patient population?

Topic	Metastatic Population	Neoadjuvant/Adjuvant population
PK	✗ Affected by patient's health status & tumour burden	✓ Homogeneous population could be selected ✗ Variability is also observed
	✓ Healthy Volunteers	
PD	✗ Clinically validated PD marker not available	
Clinical efficacy/safety	✗ •Difficult to select homogeneous group. •Need to control and stratify for multiple factors (e.g. prior use of chemotherapy, performance status…). •Population with heterogeneous characteristics affecting final clinical outcome.	✓ •Populations less likely to be confounded by baseline characteristics and external factors •Sub-group of patients with higher responses could be identified
Immunogenicity	?	?

Case study trastuzumab: Trastuzumab treatment regimens are different in different patient populations



Case study trastuzumab: Key conclusions on extrapolation of immunogenicity data

- **Immunogenicity of a biosimilar trastuzumab candidate has to be thoroughly investigated and characterized in the most sensitive setting prior to approval.**

- **The adjuvant setting is considered to be sensitive** and only this setting allows the inclusion of data from **a treatment-free follow-up phase** which **is crucial for the comprehensive characterization of the immune response of trastuzumab**.

- Therefore **extrapolation of immunogenicity data** obtained in this setting **to MBC is possible** while **extrapolation of immunogenicity data from MBC to the EBC population represents a major risk** if no safety and efficacy data are available.

EBC = Early Breast Cancer; MBC = Metastatic Breast Cancer

Establishing similarity for a rituximab biosimilar candidate: What is the sensitive population and endpoint?

Population	Ranking (homogeneous)	Endpoint/ Effect size	Rationale
Rheumatoid Arthritis	High	**ACR 20** 33 % (TNF –IR)	• Homogenous population/sub-groups available • Large treatment effect • Immunogenicity assessment feasible
1st-line DLBCL	Medium / High	**PFS 2 years** 20 %	• One treatment used (R-CHOP) • Results could be obtained relatively quickly
1st-line FL	Medium/Low	**ORR** 6 % (R-CHOP) **CR** 31 % (R-CVP)	• Heterogeneous population • Different backbones • CR difficult to assess (operational challenges)

Case Study: Previously approved Rituximab copy – Phase I/III trial on 100 DLBCL patients using R-CHOP regimen for 2 cycles

From our perspective the clinical **study is inadequate to demonstrate clinical bio-similarity** between Rituximab-RBP and this product as:

- The clinical trial population **mixes two types of populations** which have different clinical outcomes (i.e., diffuse large B cell lymphoma and follicular lymphoma)

- **ORR may not be considered a sensitive endpoint** for diffuse large B cell lymphoma nor for follicular lymphoma using CHOP chemotherapy (GELA LNH-985, updated: Feugler et al, JCO 2005; Hiddeman et al, Blood 2005; Marcus, Blood 2005)

- The **study is severely underpowered** to demonstrate equivalence of rituximab-RBP with the copied product (the study description doesn't mention if this is an equivalence, non-inferiority, or other type of design)

- **Two cycles** of therapy are **not enough to demonstrate efficacy** (RECIST guideline 1.1, Eisenhauer, EJC, 2009) nor for safety.

XXX "Evaluation of Clinical Behaviour" of an approved rituximab copy in NHL large B-cell (NHLCGB) CD20 +patients using R-CHOP regimen (Approved in LATAM)

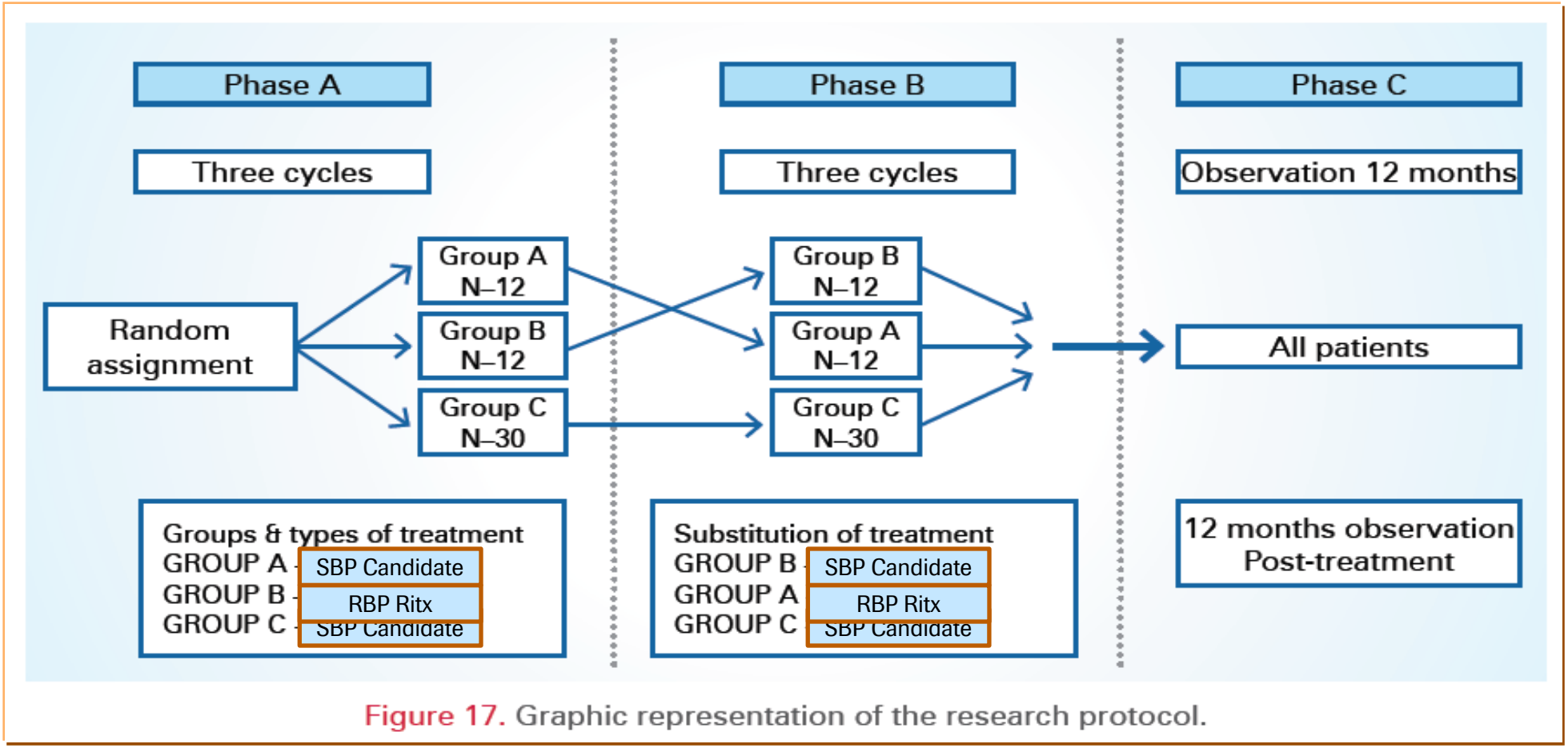
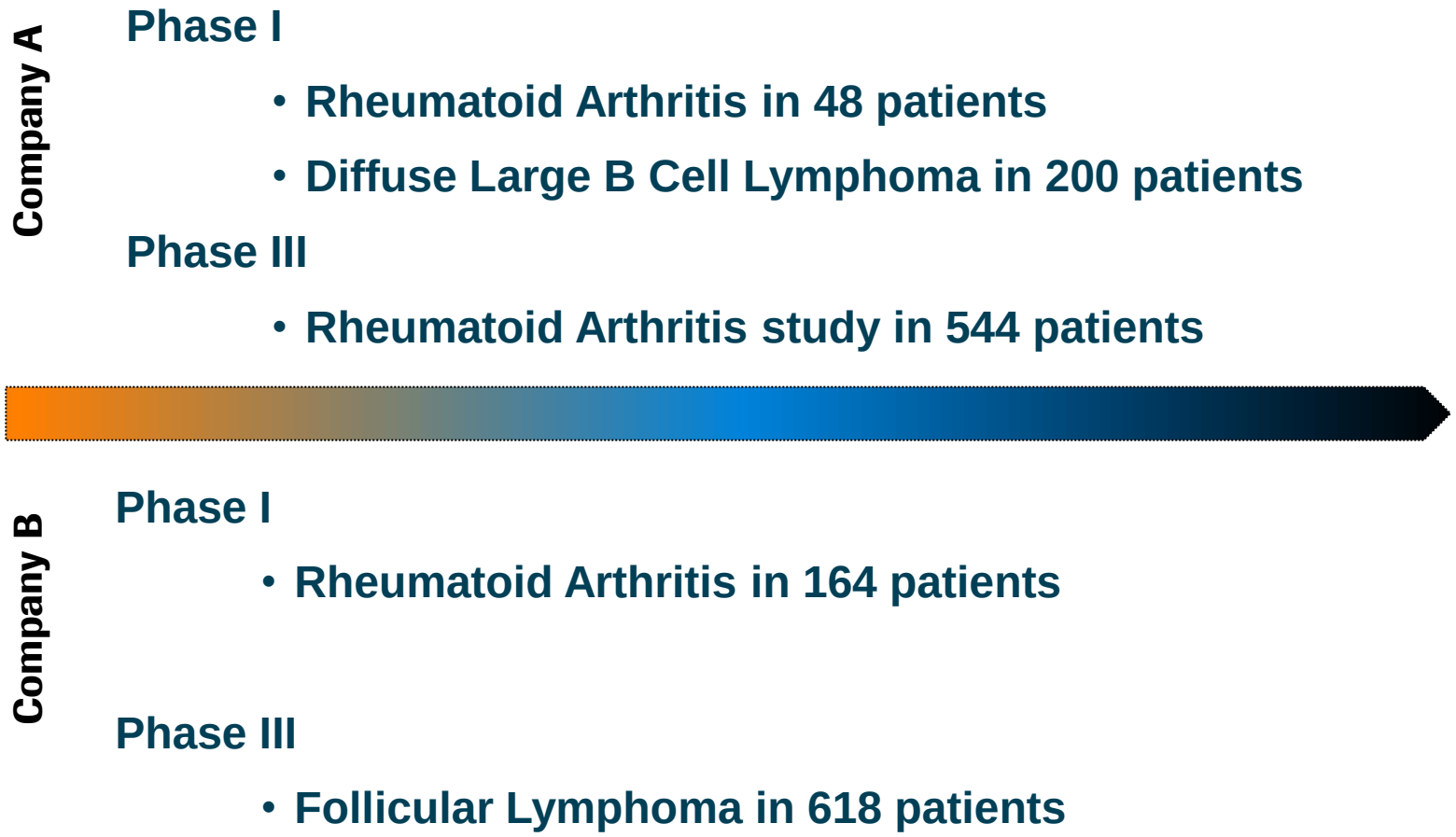


Figure 17. Graphic representation of the research protocol.

Image modified by presenter removing brand names and replace with SBP (similar biotherapeutic product) Candidate and RBP (reference biotherapeutic product) Rtx (rituximab)

Different scientific advice, or the interpretation of it, resulted in different clinical studies



Sources: *Clinicaltrials.gov http://clinicaltrials.gov/ ; company reported information*

Summary

- Biotherapeutic products, have and will provide essential and safe treatment opportunities for many diseases.
- The application of proper risk mitigation strategies during the development and marketing of similar biotherapeutics is fundamental.
- Comparative clinical testing is a key part of these strategies and has to be done in the relevant setting(s) most sensitive to potential differences in safety, efficacy and immunogenicity.
- Considering these strategies will not only minimize the risk for the patient, only those strategies will actually make the development of true similar biotherapeutics feasible.
- Unfortunately the concept of sensitive populations in the context of the clinical development of similar biotherapeutics is not well understood by many manufacturers and proper advice from NRAs may not have been taken into consideration.

Establishing biosimilarity is a challenge requiring new thinking in many areas and leaving behind old "*generic*" habits

Peter the Great
(*1672 †1725)


Thank You !